Poster I-59

A Decentralization Method for Modeling the Multiple Levels of Organization and Function Within Liver

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Development of a biological model is driven by the experimental context in which it will be used. Hence, computer models are often overfitted to a single, unique, experimental context and fail to be useful in other situations. So doing severely limits the model's usefulness, effectively blocking inferential extensions to somewhat different conditions such as a hypothesized new treatment intervention. To solve this problem, multiple, separate models of a biological system at different levels of organization are required to understand and adequately represent their behaviors. In this poster, we present the basics of a new modeling method, FURM (Functional Unit Representation Method) that attempts to address this problem. Here we focus on the primary functional unit of the liver within an in silico isolated perfused rat liver (IS-IPRL). FURM [http://biosystems.ucsf.edu/Researc/furm/index.html] decouples the various *aspects* of functional units. It uses a middle-out model design strategy that enables and encourages selection of different models. It is an example of a new class of generative biological simulation models whose components are easily joined and disconnected and are replaceable and reusable. It works by decentralizing the modeling process without requiring that all of the data be of a specific type. FURM does not require any particular formalism. Rather the experimental framework is formulated using Partially Ordered Sets. We follow four fundamental guidelines: 1) standardize interfaces to multiparadigm, multimode, and cross-trophic models, 2) use discrete interactions, 3) enable knowledge discovery by designing for an extended model life cycle, and 4) define observables that will submit to a similarity measure. A data model represents the biological system. An established in vitro liver perfusion protocol is the source of our experimental data in [*J Pharmacokin Biopharm***27:**343-82, 1999]. Two in silico system models are implemented. *RefModel* is the accepted, reference mathematical model [*JPET***297**:780–89, 2001]. *ArtModel* is our functional unit model that assumes that liver function, as a whole, is an aggregate of lobule function, that sinusoids are primarily vascular objects, and that transit time for perfusate is governed by stochastic interactions between various agents inside the vascular structures in combination with the perfusion pressure at the inlet catheter and lobule portal vein. The IS-IPRL strives to replicate the experimental procedure that has provided the experimental data. The four primary assumptions are: (1) Outflow profiles alone are lossy projections of liver behavior. Thus, physiologically accurate models are necessary to begin fully exploring the liver behavior space. (2) Hepatic vascular structure and the arrangement of lobules within a lobe can be represented by a directed graph. (3) The primary functional unit is the lobule. (4) Outflow for sucrose, but not metabolized or transported solutes, is solely a function of the extracellular (vascular cavity) space and its geometry. Within lobules agents representing sinusoidal segments (SS) are located at each graph node. Agents within each SS represent functionalities within cellular and subcellular spaces. The explicit hypothesis being tested is that the selected parameter vectors cause the model to generate output that is experimentally indistinguishable from that seen in the in vitro data. A similarity measure is used to automate the evaluation of the solution sets put forth by the models. Those results make possible automatic searches of the parameter space for regions that solve the problem by matching the in vitro data. To date different parameterizations of a mathematical model have been needed to account for outflow data for two different solutes. One IS-IPRL model now accounts for the hepatic outflow profiles of both sucrose and diltiazem and is being extended to account simultaneously for five additional drugs and to be able to shift to either of two disease states.